After the pH of the solution had stabilized between 7 and 8, the solvent was removed in vacuo (20 mmHg, 50 °C). The residue was purified by silica gel column chromatography using methanol/chloroform (1/9) as eluent to yield **10** as a white crystalline solid (0.20 g, 81%) after recrystalization from methanol/chloroform (1/4): mp 187–189 °C; TLC R_f ($CHCl_3$/methanol, 9/1) 0.35; ^1H NMR (DMSO-d_6) δ 1.77–2.66 (m, 4 H, H-2′ and H-3′), 3.35–3.69 (m, 2 H, H-5′), 3.90–4.48 (m, 1 H, H-4′), 4.99 (bs, 1 H, OH), 6.24 (t, 1 H, H-1′), 8.21 (s, 1 H, H-8), 8.53 (s, 1 H, H-2), 13.7 (bs, 1 H, SH); FAB-HRMS (m/z) calcd for $C_{10}H_{13}O_2N_4S$ (MH^+) 253.3050, found 253.3032. Anal. ($C_{10}H_{12}O_2N_4S$) C, H, N, S.

2,6-Dichloro-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-9*H*-purine (11). 2,6-Dichloropurine (0.376 g, 2 mmol), ddU (0.424 g, 2 mmol), and JA-300 cells (9 g) were mixed and incubated for 3 h in pH 6.5, 0.05 M potassium phosphate buffer at 50 °C. At the end of the reaction the mixture was centrifuged at 8000 rpm for 20 min at 10 °C. The supernatant was chromatographed on a DIAION HP-20 column and eluted with water, 20% methanol, 40% methanol, and 80% methanol. The 80% methanol fraction was evaporated to yield **11** as a white crystalline solid (0.056 g, 9.7%) following recrystalization from methanol: mp 141–143 °C; TLC R_f ($CHCl_3$/methanol, 95/5) 0.43; ^1H NMR (DMSO-d_6) δ 1.80–2.75 (m, 4 H, H-2′ and H-3′), 3.44–3.77 (m, 2 H, H-5′), 3.93–4.40 (m, 1 H, H-4′), 4.98 (t, 1 H, OH), 6.33 (t, 1 H, H-1′), 8.96 (s, 1 H, H-8); FAB-HRMS (m/z) calcd for $C_{10}H_{11}O_2N_4Cl_2$ (MH^+) 289.1602, measured 289.1584. Anal. ($C_{10}H_{10}O_2N_4Cl_2$) C, H, N, Cl.

2-Amino-9-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-9*H*-purine (12). 2-Aminopurine (0.946 g, 7 mmol) and ddU (1.48 g, 7 mmol) were added to 140 mL of pH 6.5, 50 mM potassium phosphate buffer. To the mixture were added pelleted JA-300 cells (30 g), and the mixture was incubated for 2 h at 50 °C. The cells were removed by centrifugation at 8000 rpm for 20 min at 10 °C. The supernatant was chromatographed on a DIAION HP-20 column and eluted with water and 20% and 40% methanol. The fractions of 20% and 40% methanol were concentrated and purified by silica gel column chromatography ($CHCl_3$/methanol) to give **12** (0.727 g, 44%): mp 168–169 °C; TLC R_f ($CHCl_3$/MeOH, 9/1) 0.5; ^1H NMR (DMSO-d_6) δ 1.77–2.78 (m, 4 H, H-2′, and H-3′), 3.42–3.69 (m, 2 H, H-5′), 3.78–4.29 (m, 1 H, H-4′), 4.92 (t, 1 H, OH), 6.13 (t, 1 H, H-1′), 6.51 (bs, 2 H, NH_2), 8.30 (s, 1 H, H-6), 8.57 (s, 1 H, H-8); FAB-MS (m/z) 236 (MH^+).

2′,3′-Dideoxyxanthosine, 9-(2,3-Dideoxy-β-D-*glycero*-pentofuranosyl)-9*H*-xanthosine (13). Xanthosine (4.26 g, 15 mmol; in emulsion) and ddU (3.18 g, 15 mmol) were suspended in 750 mL of pH 7.0, 0.05 M potassium phosphate buffer. The live *E. coli* JA-300 cells (150 g) were added and the reaction mixture was incubated for 4 h at 50 °C. The incubation mixture was then centrifuged at 8000 rpm for 20 min at 10 °C. The supernatant was chromatographed on a DIAION HP-20 column and eluted with water and 30% methanol. The fraction of 30% methanol was concentrated and purified by HPLC using TOSOH SC-8070 System. The purification process was monitored by a TOSOH UV-8070 P&P detector at 254 nm. A TSK gel ODS-120T column was eluted with 2% CH_3CN in pH 7.0 potassium phosphate buffer at a flow rate of 30 mL/min. The products were detected at a wavelength of 254 nm. The fraction corresponding to **13** was concentrated and desalted by DIAION HP-20 column chromatography. **13** was eluted with 50% methanol and crystallized from water–ethanol (0.20 g, 5.3%): mp >378 °C dec; λ_{max} (0.1 N NaOH) 290 nm (ϵ 8320); ^1H NMR (DMSO-d_6) δ 1.52–2.60 (m, 4 H, H-2′ and H-3′), 3.46–3.80 (m, 2 H, H-5′), 3.81–4.37 (m, 1 H, H-4′), 5.04 (t, 1 H, OH), 6.13–6.44 (dd, 1 H, H-1′), 8.32 (s, 1 H, H-8), 10.9 (bs, 1 H, NH), 11.5 (bs, 1 H, NH); ^{13}C NMR (D_2O + NaOD) δ 27.6 (C-3′), 35.2 (C-2′), 65.8 (C-5′), 85.2 (C-4′), 89.7 (C-1′), 109.5 (C-5), 143.5 (C-8), 161.7 (C-4), 163.6 (C-2), 164.5 (C-6); FAB-HRMS (m/z) calcd for $C_{10}H_{13}O_4N_4$ (MH^+) 253.0937, found 253.0900. Anal. ($C_{10}H_{12}O_4N_4 \cdot 0.5H_2O$) C, H, N.

2′,3′-Dideoxynebularine, 9-(2,3-Dideoxy-β-D-*glycero*-pentofuranosyl)-9*H*-purine (14). Purine (0.84 g, 7 mmol), ddU (1.49 g, 7 mmol), and JA300 cells (32 g) were mixed and incubated for 4 h in pH 6.5, 0.05 M potassium phosphate buffer at 50 °C, followed by centrifugation. The supernatant was chromatographed on a DIAION HP-20 column and eluted with water and 100% methanol. The methanol fraction was evaporated and purified by silica gel column chromatography using methanol/chloroform (1/9) as eluent to yield the title compound as a white crystalline solid (0.66 g, 43%) after recrystallization from methanol: mp 157–159 °C; TLC R_f ($CHCl_3$/methanol, 9/1) 0.60; ^1H NMR (DMSO-d_6) δ 1.80–2.80 (m, 4 H, H-2′ and H-3′), 3.38–3.77 (m, 2 H, H-5′), 3.82–4.39 (m, 1 H, H-4′), 4.97 (t, 1 H, OH), 6.39 (t, 1 H, H-1′), 8.84 (s, 1 H, H-6), 8.94 (s, 1 H, H-8), 9.17 (s, 1 H, H-2): FAB-MS (m/z) 221 (MH^+). Anal. ($C_{10}H_{12}O_2N_4$) C, H, N.

Registry No. **1**, 132194-21-9; **2**, 122970-35-8; **3**, 132194-22-0; **4**, 132194-23-1; **5**, 132194-24-2; **6**, 120503-34-6; **7**, 132194-25-3; **8**, 120503-37-9; **9**, 132194-26-4; **10**, 126502-10-1; **11**, 132194-27-5; **12**, 107550-74-3; **13**, 132194-28-6; **14**, 126502-08-7.

Synthesis and in Vitro Evaluation of 2,3-Dimethoxy-5-(fluoroalkyl)-Substituted Benzamides: High-Affinity Ligands for CNS Dopamine D_2 Receptors[1]

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A number of 2,3-dimethoxy-5-(fluoroalkyl)-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamides (with or without a 6-hydroxy group) were synthesized and evaluated as dopamine D_2 receptor ligands. The parent acids were synthesized via the Claisen rearrangement of the appropriate *O*-allyl ethers, which were derived from *o*-vanillic acid or 2,3-dimethoxysalicylic acid. A decrease in reactivity was found to be characteristic of pentasubstituted benzoates, and difficulties were encountered with the introduction of fluorine onto the ethyl side chains. The (fluoroethyl)- and (fluoropropyl)salicylamides were 5 times more potent than the corresponding benzamides in inhibiting [^3H]spiperone binding to the D_2 receptor. These (fluoroalkyl)salicylamides are of potential value for in vivo positron emission tomography (PET) studies upon the basis of their relatively selective, high potency binding affinity for the D_2 receptor.

During the past decade the binding properties of a variety of benzamides and salicylamides containing *N*-[(1-alkyl-2-pyrrolidinyl)methyl] side chains have been reported.[2-5] Many of these amides are selective and potent

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† University of California, Berkeley.

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(1) Portions of this work were presented at the 198th American Chemical Society Meeting, Medicinal Chemistry Division, Miami, FL, Sept 1989.

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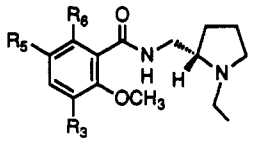
0022-2623/91/1834-1612$02.50/0

Chart I

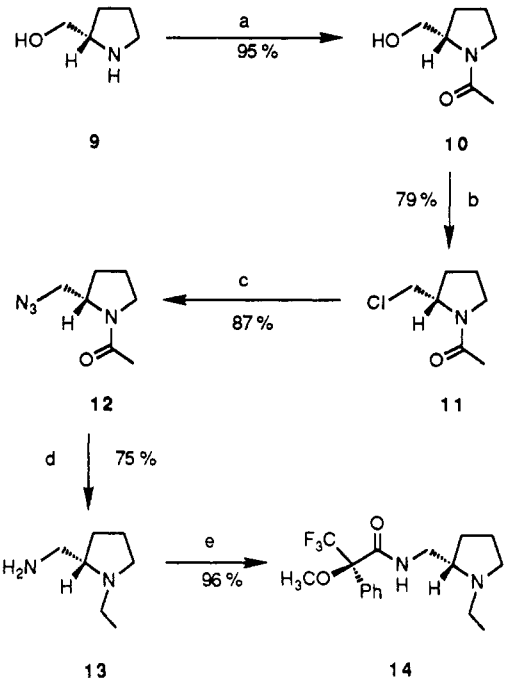


Compound	R_3	R_5	R_6
Raclopride	Cl	Cl	OH
Eticlopride	Cl	CH_2CH_3	OH
Epidepride	OCH_3	I	H
Ioxipride (NCQ 298)	OCH_3	I	OH
1	OCH_3	$CH_2CH_2CH_2F$	H
2	OCH_3	CH_2CH_2F	H
3	OCH_3	$CH_2CH_2CH_2F$	OH
4	OCH_3	CH_2CH_2F	OH
5	OCH_3	Br	H
6	OCH_3	H	H
7	OCH_3	$CH_2CH_2CH_3$	H
8	OCH_3	$CH_2CH_2CH_3$	OH

dopamine D_2 receptor antagonists, displaying reduced extrapyramidal side effects compared to butyrophenones such as haloperidol.[4,6,7] Recent reports have identified epidepride, ioxipride, and 5-bromo-2,3-dimethoxybenzamide **5** (Chart I) as high-affinity D_2 receptor ligands.[8-11] These studies have revealed the 2,3-dimethoxy-5-halobenzene substitution pattern as a key structural element contributing to high binding potency. Additionally, the lipophilicity and binding characteristics of benzamides can be modulated by replacement of the 5-halogen atom with alkyl groups.[4,5] The preservation of biological activity and the altering of lipophilic properties with the replacement of aromatic halogen atoms with alkyl[12] and fluoroalkyl[13] groups has also been described for the potent 2,5-dimethoxy-4-substituted-amphetamine hallucinogens. By analogy, studies of the structure–activity relationships between 5-halo- and 5-(fluoroalkyl)benzamides could identify D_2 ligands with optimal binding, lipophilic, and metabolic properties for use as effective in vivo imaging agents of the dopamine D_2 receptor system.

The radiolabeled salicylamide [^{11}C]raclopride (Chart I) has been utilized as a positron emission tomography (PET) imaging agent of CNS dopamine D_2 receptors.[14,15] This ligand has increased selectivity and decreased nonspecific binding properties compared to spiperone and spiperone derivatives.[16-18] Because radioligands containing the longer lived ^{18}F radionuclide have advantages for PET studies over those containing ^{11}C for PET studies,[19] *N*-fluoroalkyl derivatives of the pyrrolidine ring of raclopride have been synthesized and evaluated.[20-22] These analogues displayed a much lower affinity for the D_2 receptor than the parent compound and are less useful for in vivo studies.[19,23] More encouraging in vivo results have been reported[24] when the radiolabeled fluoroalkyl group is placed on the phenyl ring. In order to identify the most promising candidate(s) for future quantitative PET studies of the dopamine D_2 receptor, we synthesized the fluoro-

Scheme I[a]



[a] Conditions: (a) Ac_2O, K_2CO_3; (b) $SOCl_2$; (c) NaN_3, KI; (d) $LiAlH_4$; (e) (*R*)-$C_6H_5C(CF_3)(OCH_3)CO_2H$, $(COCl)_2$.

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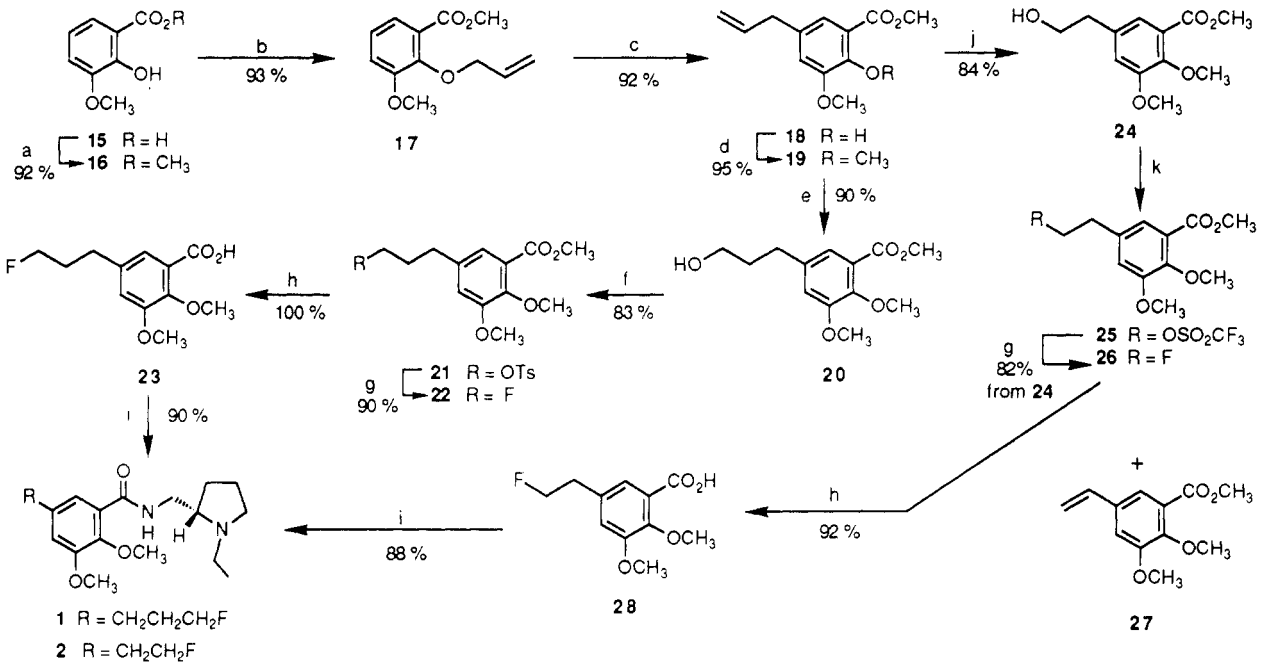
Scheme II[a]



[a] Conditions: (a) CH_3OH, H_2SO_4; (b) allyl bromide, K_2CO_3; (c) 220 °C; (d) CH_3I, K_2CO_3; (e) 9-BBN; NaOH, H_2O_2; (f) TsCl, pyridine; (g) n-Bu_4NF; (h) NaOH, H_2O, THF; (i) $(COCl)_2$, DMF; **13**; (j) O_3; $NaBH_4$; (k) Tf_2O, 2,6-lutidine.

alkylated benzamides and salicylamides 1–4 (Chart I) and evaluated their in vitro binding properties.

Results and Discussion

Chemistry. Initial attempts to synthesize the 5-fluoroalkyl compounds 1–4 involved the regiospecific introduction of an alkyl side chain onto benzamide substrates at the 5-position. Preliminary studies of the lithium for halogen exchange[5,25,26] of the 5-bromobenzamide **5**, or a precursor[27,28] to **5**, followed by trapping with appropriate alkyl electrophiles[13] resulted in low alkylation yields, particularly for compounds containing 6-position oxygen substituents. Therefore, the appropriately substituted benzoic acid precursors were first prepared and subsequently coupled with (*S*)-2-(aminomethyl)-1-ethylpyrrolidine (**13**) (Scheme I) to form the amide linkage. The 5-position alkyl side chains of **1** and **2** are situated para to the 2-methoxy substituent while those for **3** and **4** are ortho to the 6-hydroxyl group suggesting that these substitution patterns could be achieved by Claisen rearrangements of aryl allyl ethers.[29]

An essential component in the syntheses of amides 1–4 was the pyrrolidine **13**. We improved the existing synthetic route[30,31] to **13** by functionalization of the pyrrolidine nitrogen by an acylation rather than alkylation reaction[32] according to the synthetic plan shown in Scheme I. The (*S*)-2-(hydroxymethyl)pyrrolidine (**9**), either commercially available or readily prepared from L-proline,[33] was selectively acetylated, producing the amide **10**. Chlorination, followed by azide formation, and then hydride reduction were achieved by minor variations of reported procedures.[30,34] By this sequence, **13** was generated on a multigram scale and in an overall yield of 49% from **9**. Optical purity was determined by derivatizing both racemic and optically active **13** with (*R*)-(+)-α-methoxy-α-[(trifluoromethyl)phenyl]acetyl chloride (MTPA acid chloride)[35,36] to form the MTPA amide **14** and quantifying the resulting diastereomeric composition by both high resolution ^1H NMR (500 MHz) spectroscopy and capillary gas chromatography. These data, combined with experiments to determine the limits of detection, confirmed that the synthetically derived **13** had an enantiomeric excess (ee) of greater than 99.5%. Enantiomerically enriched **13** was also obtained by selective recrystallization as the D-tartrate salt.[37] Three sequential recrystallizations provided **13** in >99.5% ee. Since the amide syntheses do not involve the chiral center, it was assumed that the benz-

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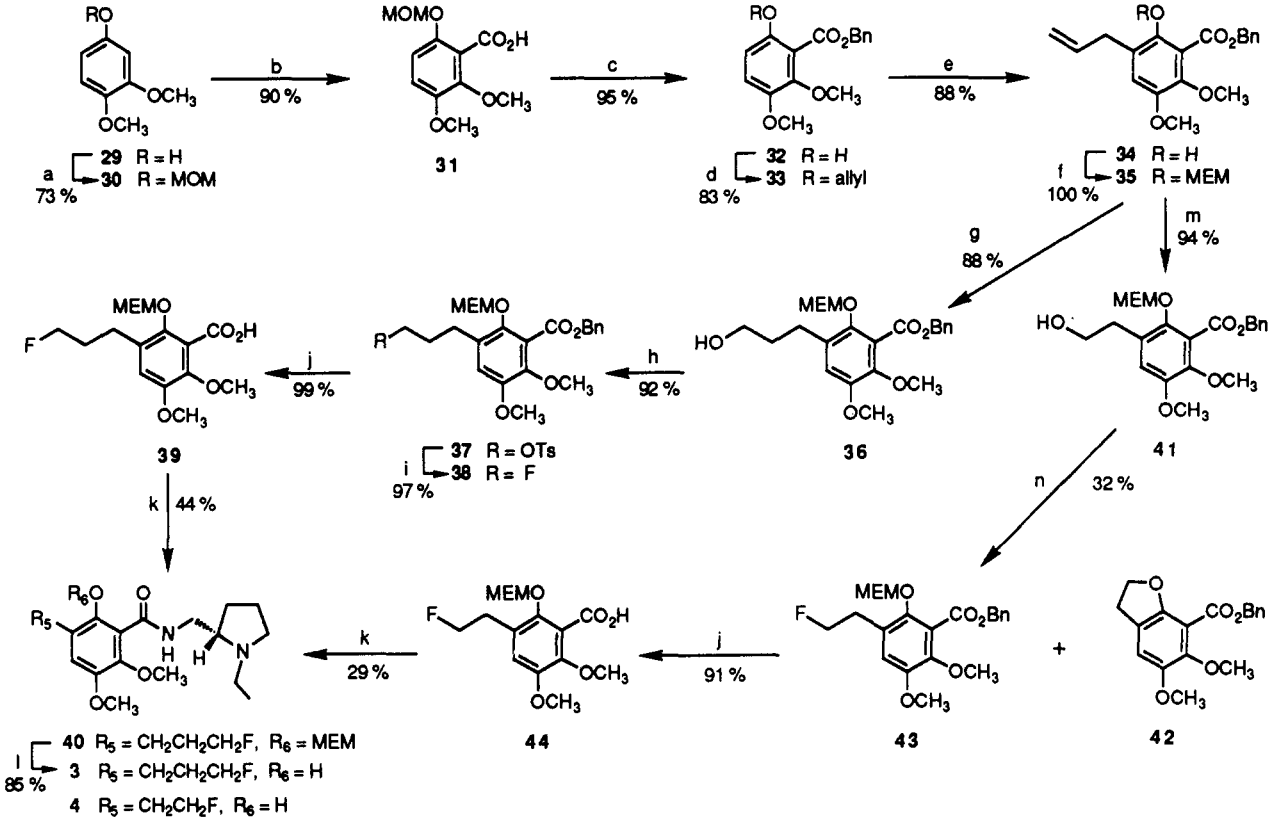
Scheme III[a]



[a] Conditions: (a) *n*-BuLi, MOMCl; (b) *n*-BuLi, TMEDA; CO_2; (c) $(COCl)_2$, DMF; BnOH; (d) allyl bromide, K_2CO_3; (e) 205 °C; (f) NaH, MEMCl; (g) 9-BBN; NaOH, H_2O_2; (h) TsCl, pyridine; (i) *n*-Bu_4NF; (j) H_2, Pd/C; (k) $(COCl)_2$, DMF; **13**; (l) $TiCl_4$; (m) O_3, MeOH; $NaBH_4$; (n) Et_2NSF_3.

amides and salicylamides derived from **13** also had optical purities of >99.5% ee.

The synthesis of benzamide **1** (Scheme II) commenced with the esterification of the commercially available 3-methoxysalicylic acid (**15**). The methyl ester **16**[38] was converted to the allyl ether **17** and then rearranged to afford the para Claisen product **18**. The regiospecificity of the alkyl side chain introduction was confirmed by examination of the ^1H NMR spectrum of **18** as the aromatic proton coupling constants of 1.5 Hz were consistent with a meta relationship[39] for the two remaining ring protons. Methylation of **18** provided the key intermediate **19**, at which point the syntheses of **1** and **2** diverged. Reduction of the propenyl side chain of **19** with 9-borabicyclo-[3.3.1]nonane (9-BBN)[40] was followed by oxidative workup to afford the propanol **20**. Conversion of **20** to the fluoride **22** was accomplished[41] by the formation of tosylate **21** which was then subjected to fluoride substitution (tetrabutylammonium fluoride, TBAF). Saponification of **22** afforded the acid **23** which was transformed to the benzamide **1** by first generating the corresponding acid chloride (not isolated) followed by coupling to **13**. Benzamide **1** was thus produced from **15** in an overall yield of 45%.

The (fluoroethyl)benzamide **2** was also produced from **19**. Oxidative degradation of the alkene side chain of **19** with ozone followed by reductive workup afforded the hydroxyethyl intermediate **24**. Transformation of **24** to the reactive triflate **25** (not isolated) was followed by fluoride anion displacement at room temperature and chromatographic separation to yield the fluoroethyl derivative **26**. Attempts to achieve the same transformation with the tosylate ester required elevated temperature and resulted in the formation of a mixture of **26** and the styrene **27**.[13] Saponification of **26** followed by coupling to **13** afforded the benzamide **2**. The preparation of **2** was achieved in an overall yield of 42% from **15**.

The syntheses of salicylamides **3** and **4** involved the synthetic approach outlined in Scheme III in which the 5-alkyl side chain was introduced adjacent to four contiguous aryl substituents by the Claisen rearrangement of a 6-position phenyl allyl ether (**33** → **34**). In this manner, the problems of steric congestion[42] of hydroxyl group introduction[43] and 6-methoxy group demethylation[5] were avoided. The two synthetic routes diverged at intermediate **35**, which contained a benzyl ester protecting group as a result of unsuccessful attempts to employ both the methyl and *tert*-butyl esters. Steric hinderance at the ester sites of the salicylic intermediates was striking as attempted saponification of the methyl ester form of **38** proved impossible under conditions compatible with preserving the other functionalities on the molecule. In contrast, the tetrasubstituted methyl benzoate **22** was readily hydrolyzed (Scheme II). The *tert*-butyl ester form of **33** was not stable to Claisen rearrangement conditions (200 °C) as isobutylene and the corresponding carboxylic acid were formed.

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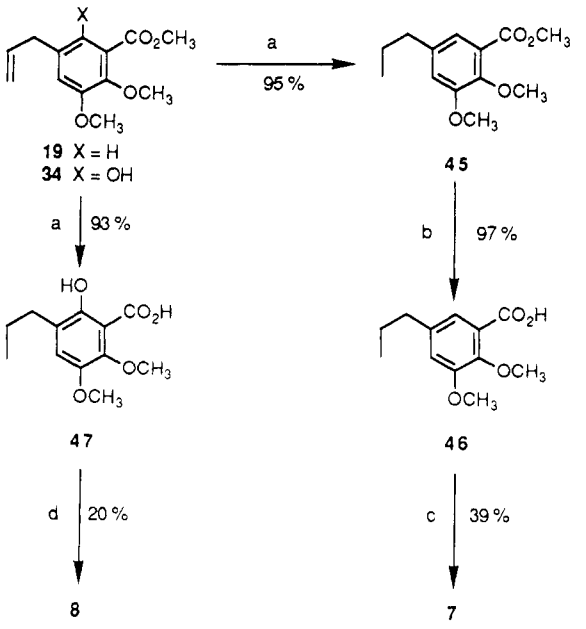
Scheme IV[a]



[a] Conditions: (a) H_2, Pd/C; (b) NaOH, THF; (c) DCC, HOBT, 13; (d) $SOCl_2$, DMF; 13.

Etherification of **29**[44] provided the methoxymethyl (MOM) ether **30**, which was treated with *n*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine (TMEDA), and the resultant anion was trapped with carbon dioxide to produce the benzoic acid **31** in high yield.[45] The conversion of **31** to the benzyl salicylate **32** was accomplished by formation of the acid chloride (not isolated) followed by addition of an excess of benzyl alcohol.[46] The Claisen rearrangement precursor **33** was prepared and then rearranged to afford the phenol **34**. Protection of **34** with the 2-(methoxyethoxy)methyl (MEM) group provided **35** which was elaborated to **38** by the sequence noted earlier. Hydrogenolysis of the benzyl ester **38** produced **39**, which was converted to the acid chloride (not isolated) and then to the MEM-protected salicylamide **40**.[47] These amide forming conditions are noteworthy since alternate reaction conditions, using thionyl chloride and DMF, required elevated temperatures and resulted in decomposition. The use of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) also proved unsuccessful apparently as a result of increased steric hindrance of the pentasubstituted benzoic acid **39**. Finally, removal of the MEM group ($TiCl_4$)[48] afforded the salicylamide **3** in an overall yield of 13% from **29**.

Formation of the 5-(2-fluoroethyl)-6-hydroxybenzamide **4** was more problematic than the analogous benzamide **2**.

(44) Matsumoto, M.; Kobayashi, H.; Hotta, Y. *J. Org. Chem.* **1984**, *49*, 4740.
(45) The presence of TMEDA was essential for successful formation of the aryl anion.
(46) It is likely that during the formation of the acid chloride with oxalyl chloride, the resulting HCl promoted the acid hydrolysis of the MOM ether group.
(47) The use of oxalyl chloride and DMF allowed acid chloride formation to occur at room temperature. The stoichiometry of reagents was critical in order to avoid concomitant phenol deprotection. When the amount of DMF employed was equimolar with oxalyl chloride (200 mol %), the MEM protecting group remained intact. When a catalytic quantity (20 mol %) of DMF was used, the MEM group was removed and low yields of amide coupling products were obtained.
(48) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

Table I. Potency of Compounds for Dopamine D_2 Receptors in the Presence or Absence of Sodium Chloride[a]

compd	K_i, nM without NaCl	K_i, nM with NaCl
chlorpromazine	1.77 ± 0.14	2.19 ± 0.44
raclopride	32.8 ± 5.9	8.29 ± 0.08
eticlopride	0.99 ± 0.04	0.19 ± 0.02
epidepride	0.66 ± 0.09	0.27 ± 0.04
1	4.40 ± 0.27	1.17 ± 0.09
2	5.27 ± 1.66	1.41 ± 0.11
3	0.80 ± 0.09	0.25 ± 0.01
4	0.77 ± 0.19	0.24 ± 0.03
5	0.76 ± 0.06	0.20 ± 0.02
6	66.0 ± 0.0	ND[b]
7	6.98 ± 2.07	ND
8	1.28 ± 0.10	ND
(*R*)-**2**	>10 μM	ND
(*R*)-**3**	>10 μM	ND

[a] Striatal membranes were labeled with [^{3}H]spiperone. See methods for details. The IC_{50}, from which the K_i was calculated, was determined from a Hill plot of seven data points in triplicate. All data represent the mean ± SEM for three or more individual determinations performed on separate days. [b] ND = not determined.

Table II. Potency of Selected Compounds for α_2 Adrenoreceptors[a]

compd	K_i, nM
phentolamine	1.4
epidepride	5.0
3	11.1
4	9.5

[a] Membranes from rat frontal cortex membranes were labeled with [^{3}H]atipamezole. See methods for details. The IC_{50} from which the K_i was calculated was determined from a Hill plot of seven data points in triplicate. The assay was repeated twice with similar results.

Attempted fluoride ion (TBAF) displacement of the corresponding tosylate of **41** resulted in quantitative elimination to the respective styrene product.[49] Formation of the more reactive triflate derivative of **41** and attempted fluoride displacement led to deprotection of the MEM group and cyclization to benzofuran **42**.[50] Ultimately, a modest amount of **43** as well as the side product **42** were obtained by treating **41** with diethylamidosulfur trifluoride (DAST).[51] By using this procedure, the salicylamide **4** was obtained from **29** in an overall yield of 4%.

For in vitro binding studies, the *R* enantiomers of **2** and **3** were synthesized in fashions similar to those described above by using (*R*)-2-(aminomethyl)-1-ethylpyrrolidine, which was obtained in >99% ee from three sequential recrystallizations of the L-tartrate salt.[37] The benzamides[25] **5** and **6** were generated by the acid chloride mediated amide couplings of 5-bromo-2,3-dimethoxybenzoic acid[27] and the commercially available 2,3-dimethoxybenzoic acid, respectively. The syntheses of the *n*-propylbenzamide **7**

(49) (a) Fluoride ion can function as a base, thereby promoting elimination processes. See: Clark, J. H. *Chem. Rev.* **1980**, *80*, 429. (b) The propensity for ethyl (2-phenyl)tosylates to undergo elimination is promoted by a β-aromatic ring (March, J. *Advanced Organic Chemistry*; Wiley: New York, 1985; p 894). In contrast, the propyl (3-phenyl)tosylate substrates, in which the aromatic ring is in the γ-position, do not afford elimination side products.
(50) Deprotection of the MEM ether could have occurred during the formation of the triflate ester since small quantities of triflic acid might have been generated. Additionally, it is possible that fluoride ion functioned as a base, generating the phenoxide anion which underwent cyclization.
(51) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

and -salicylamide 8[5] were accomplished by the routes outlined in Scheme IV. Hydrogenation of 19 was followed by saponification and then amide formation by the DCC/HOBT method to provide 7 (36% overall yield). Similar treatment of 34 yielded the acid 47 which was coupled to 13 with thionyl chloride and DMF to afford 8 (19% overall yield).

In Vitro Binding Studies. The potency and selectivity of the compounds for rat striatal dopamine receptors were evaluated by using radioligand binding methodology. None of the benzamides or salicylamides had appreciable activity (i.e., $K_i > 1$ μM) in competing for D_1 receptors labeled by [^{3}H]SCH 23390. Conversely, five of the compounds (eticlopride, epidepride, 3, 4, and 5) had very high affinity (i.e., $K_i < 1$ nM) for D_2 receptors labeled by [^{3}H]spiperone (Table I). Compounds 1 and 2 (the (fluoroalkyl)benzamides) were significantly less potent for the D_2 receptor, by a factor of about 5, than the corresponding salicylamides (compounds 3 and 4). The *n*-propyl compounds displayed similar differences in potency, with the salicylamide 8 being about 5 times more potent than the benzamide 7. Substitution at the 5-position of all the benzamides with lipophilic halogen, alkyl, or fluoroalkyl groups resulted in compounds significantly more potent than the 5-H compound 6.[4,5] Analysis of the kinetics of the benzamides and salicylamides in competing for [^{3}H]-spiperone binding sites resulted in Hill coefficient (n_H) values not significantly different from 1.0; this is consistent with these compounds competing with a single or relatively homogeneous population of radioligand binding sites. These data demonstrate that compounds 3 and 4 have high potency for D_2 receptors and clear selectivity (more than three orders of magnitude) in favoring D_2 over D_1 receptors. These properties are of potential value for in vivo PET studies of the D_2 receptor since endogenous dopamine may effectively inhibit the binding of less potent ligands, such as [^{11}C]raclopride, at the D_2 receptor.[52] Since the K_i's of compounds 3 and 4 are about 40-fold lower than that of raclopride, their binding will likely be less inhibited by endogenous dopamine.

Compounds 1–4 were also found to have no significant potency (IC_{50}'s > 1 μM) at 5-HT_2 or α_1-adrenergic receptors labeled by [^{3}H]ketanserin and [^{3}H]prazosin, respectively. Because epidepride has been reported to have α_2-adrenergic potency, [^{3}H]atipamezole[53] was utilized to assess the potency of compounds 3 and 4 at this class of receptor. As can be seen in Table II, both 3 and 4 had significant potency for [^{3}H]atipamezole binding sites. This raises the issue of whether the α_2-adrenergic potency of these compounds will adversely impact their utility in imaging studies. Several factors suggest that this will not compromise the use of these compounds. The K_i's for compounds 3 and 4 at α_2 sites were ca. 10 nM; the potency of these compounds at D_2 receptors was about 10–15 times greater than this in the absence of sodium ions, and 40 times greater in the presence of sodium ions. Coupled with what is known about the concentrations of the α_2 receptor in various brain regions,[54] this selectivity, while not ideal, should not significantly impact the utility of 3 and 4 as ligands for PET studies. Relative to other commonly used ligands (e.g., spiperone[55] or its derivatives[16]), compounds 3 and 4 have essentially no potency at serotonergic sites.

It has been reported[9] that the presence of 50 mM sodium chloride caused a decrease in the K_D of [^{125}I]epidepride, which is consistent with an earlier report[56] using [^{3}H]-sulpiride. The K_D of epidepride was observed to decrease from 537 to 32 pM, whereas the K_D of [^{3}H]spiperone was essentially unchanged under similar conditions.[9] It was hypothesized that this change was due to sodium-mediated receptor isomerization, resulting in increased potency of [^{125}I]epidipride. Because these findings were based largely on the use of the GH_4ZR_7 cell line transfected with the D_2 dopamine receptor, the data were not confounded by receptor multiplicity issues present when homogenized brain tissue are used. On the basis of these findings, we determined the potencies of several key compounds in competing for [^{3}H]spiperone sites in both the absence and presence of NaCl. When the assay buffer contained 50 mM sodium chloride, a 4-fold increase in the potency of all of the tested benzamides and salicylamides in competing for the butyrophenone [^{3}H]spiperone was observed (Table I). Conversely, the potency of chlorpromazine and spiperone[9] in competing for [^{3}H]spiperone binding sites was unaffected by the NaCl. This 4-fold increase in the apparent potency of the benzamides is considerably smaller in magnitude than that previously reported.[9] This difference may result from the choice of buffers in the assay system,[57] the tissue used (GH_4ZR_7 vs striatal membranes), or both. It is clear from the present study and earlier work[9,56] that sodium ion dramatically increases the D_2 binding potency of benzamides, but not phenothiazines or butyrophenones.

The K_D of [^{125}I]epidepride, in the presence of NaCl, was reported[9] to be 20–40 pM. Conversely, the K_i we have calculated for epidepride by its competition for [^{3}H]spiperone sites was nearly an order of magnitude greater than this (Table I). According to mass action principles, there should be excellent agreement between dissociation constants whether calculated by direct or indirect techniques if these drugs are labeling the same population(s) of receptors in the same way. One possible explanation might have involved differences in the behavior of [^{125}I]epidepride in brain membranes with our buffer systems vs the GH_4ZR_7 expression system. Because saturation isotherms with [^{125}I]epidepride indicated a K_D essentially identical with that previously reported[9] (ca. 40 pM; data not shown), methodological procedures cannot account for this discrepancy. Although they did not explicitly highlight the finding, a series of recent papers[5,10,26] also reported that benzamides and salicylamides demonstrated nearly an order of magnitude lower potency in competing for [^{3}H]-spiperone sites than for [^{3}H]raclopride sites.

Several hypotheses might explain why there are differences in the apparent potency of benzamides and salicylamides in competing against two different radioligands. For one, the sites labeled by these ligands may be distinct molecular entities. In this regard it should be noted that 50 nM NaCl increased the number of [^{125}I]epidepride binding sites (i.e., B_{max}), but did not affect the number of [^{3}H]spiperone binding sites (data not shown). Not only have several distinct molecular forms of the D_2 receptor been cloned,[58-61] but another dopamine receptor has also

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been cloned and termed D_3.[62] While this D_3 receptor has a pharmacology similar to those receptors generically termed D_2, it is reported to have markedly greater affinity for certain benzamides. It is also possible that, even with a single-receptor population, some classes of ligands interact with different structural features of the receptor. These questions will be able to be addressed more definitively in the near future as molecular probes and better expression systems become available. These issues are of critical importance to the use of these ligands for in vivo imaging studies. In addition to the differences we have noted for their in vitro interaction with receptors, it is well known that there are interesting psychopharmacological differences between benzamides and butyrophenones.[4-7] The successful application of these agents to PET studies requires that regional concentrations of the radioligands reflect in vivo D_2 receptor densities. If the benzamides interact with different allosteric sites on the D_2 receptor,[9,63] their binding to a site distinct from that to which spiperone binds should not diminish the usefulness of these compounds as ligands for PET dopamine D_2 studies. In this regard, in vitro studies[64] using [^{3}H]spiperone and [^{3}H]raclopride have yielded similar D_2 receptor densities for the two ligands in rat striatal tissue. If the sites labeled by benzamides are distinct molecular species, the physiological and pharmacological significance of their binding and distribution requires additional study and clarification.

Conclusions. The 5-(fluoroalkyl)benzamides (**1** and **2**) and 5-(fluoroalkyl)-6-hydroxybenzamides (**3** and **4**) were prepared by synthetic routes which were based on the type of substituents present at the 6-position of the aromatic rings. Common to both approaches were Claisen rearrangements of aryl allyl ethers which provided the highly functionalized aromatic intermediates. Comparison of overall synthetic yields reveals that benzamides **1** and **2** were produced more efficiently. The more encumbered syntheses of the salicylamides **3** and **4** were a result of the decreased reactivities of the more sterically hindered pentasubstituted benzoic esters and acids as well as the propensity of *o*-(fluoroalkyl)phenols to undergo cyclizations. Furthermore, the ease by which the fluorine atoms were introduced at the terminal carbon atom of the propyl aromatic side chains relative to the ethyl counterparts was significant and is a consideration for future [^{18}F]-labeled radiopharmaceutical development.

The presence of sodium chloride lowered the K_i's of the benzamides and salicylamides by about a factor of 4 compared to its absence. Direct and indirect binding techniques resulted in an inconsistency in the K_D value of [^{125}I]epidepride vs the K_i value of epidepride measured against [^{3}H]spiperone. Several different hypotheses could explain these discrepancies, and these issues may be addressed in future studies by using more defined in vitro binding systems. Compounds **3** and **4** were inactive at D_1, 5-HT_2, and α_1 rat brain binding sites, but had significant affinity for α_2 binding sites. The α_2 binding potency of compounds **3** and **4** was more than an order of magnitude less than their D_2 potency and should not significantly diminish the usefulness of these ligands as imaging agents. The (fluoroalkyl)salicylamides (**3** and **4**) were five times more potent in inhibiting [^{3}H]spiperone binding to the D_2 receptor than were the corresponding (fluoroalkyl)benzamides (**1** and **2**) and were equipotent with the 5-iodo- and 5-bromobenzamides (epidepride and **5**). These in vitro properties indicate that ^{18}F-labeled forms of the (fluoroalkyl)salicylamides **3** and **4** hold considerable potential as in vivo PET imaging agents.

Experimental Section

General Methods. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium and benzophenone; methylene chloride was distilled from CaH_2, all immediately prior to use. Pyridine and dimethylformamide (DMF) were distilled from CaH_2 and then stored over 4 Å molecular sieves. Solutions of *n*-butyllithium were titrated[65] before use. Other solvents and reagents were used as received from commercial suppliers, unless otherwise specified. Calcined K_2CO_3 was purchased from LCP Chemicals and Plastics, Inc., Ashtabula, OH. Recrystallization of *p*-toluenesulfonyl chloride was according to the method of Fieser.[66] Aqueous basic and hydrogen peroxide solutions noted in percent were formulated on a weight to weight basis. Kieselgel 60 F_{254} aluminum-backed plates (E. Merck) were used for thin-layer chromatography. Some TLC plates were developed with ninhydrin (11 mM in EtOH) or phosphomolybdic acid (20 mM in 95% aqueous EtOH) solutions. Column chromatography was performed with Kieselgel 60 (70–230 mesh) silica gel for gravity columns and Kieselgel 60 (230–400 mesh) silica gel (E. Merck) for flash columns. High-performance liquid chromatography (HPLC) purifications were performed with a Waters Associates M45 pumping system and R401 differential refractometer, Rheodyne injector and a Whatman M9-Partisil (silica) column. The HPLC and column chromatography solvents employed were glass distilled, and solvent mixtures are reported as volume to volume ratios. All nonaqueous reactions were performed in oven-dried glassware under an atmosphere of argon. Analytical capillary gas chromatography (capillary GLC) employed a 30-m (0.53 mm i.d.) Supelco SPB-1 (0.25 μm dimethylpolysiloxane) capillary column with a HP 5880A gas chromatograph with FID detection. Kugelrohr distillation temperatures refer to the oven temperature range during which distillate was collected and may not represent precise boiling points. Melting points are uncorrected and were taken on a Mel-Temp apparatus.

The NMR spectra were recorded with a Bruker AM 500 spectrometer. Proton ^{1}H (500 MHz, TMS internal reference) and carbon ^{1}H-decoupled ^{13}C NMR (126 MHz, internal reference $CDCl_3$, 77.0 ppm) spectra were recorded in $CDCl_3$. NMR data are presented as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constant(s) in Hertz. Where 135° DEPT ^{13}C NMR data are given, an asterisk denotes an inverted (CH_2) resonance. Infrared (IR) spectra were recorded as thin films on NaCl plates with a Perkin-Elmer 1310 infrared spectrophotometer, and optical rotations were measured on a Perkin Elmer 241 polarimeter. Electron impact (EI) and fast-atom bombardment (FAB) mass spectra were recorded on a Kratos MS-50 instrument. Elemental analyses were obtained from the Microanalytical Laboratory of the Department of Chemistry, University of California, Berkeley, and were within ±0.4% of calculated values, unless otherwise noted.

For the binding studies, [^{125}I]epidipride and [^{3}H]SCH 23390 were synthesized as described previously.[9,67] [^{3}H]Spiperone,

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[^{3}H]prazosin, and [^{3}H]ketanserin were purchased from New England Nuclear (Boston, MA); [^{3}H]atipamezole was received as a gift (Farmos Group Ltd., Turku, Finland). The following drugs were obtained as gifts: SCH 23390 (Schering Inc., Bloomfield, NJ); ketanserin tartrate (Janssen Pharmaceutica, New Brunswick, NJ); chlorpromazine (Smith, Kline and French, Philadelphia, PA); and raclopride (Astra Pharmaceuticals, Sodertalje, Sweden). Epidepride was synthesized by methods modified from the literature.[26]

(*S*)-1-Acetyl-2-(hydroxymethyl)pyrrolidine (10). (*S*)-2-(Hydroxymethyl)pyrrolidine[33] (**9**) (20.40 g; 201.7 mmol) was dissolved in 240 mL of CH_2Cl_2, 27.87 g (100 mol %) of calcined K_2CO_3 was added, and the mixture was stirred and cooled to approximately 0 °C. Acetic anhydride (20.0 mL, 105 mol %) was then added dropwise over 5 min. After 90 min the solids were filtered off and washed with CH_2Cl_2 (100 mL). The combined filtrates were washed with 50 mL of 1 M H_3PO_4, the aqueous phase was back-extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford **10** (27.40 g, 95%) as a yellow liquid. The material was homogeneous by TLC (R_f = 0.31; $CH_3OH/CHCl_3$, 1:9; ninhydrin development) and was routinely used without further purification. Kugelrohr distillation of this material (119–121 °C, 0.6 mmHg) afforded a colorless liquid (lit.[30] bp 95–96 °C, 0.1 mmHg): ^{1}H NMR δ 5.17 (br s, 1 H), 4.18 (m, 1 H), 3.47–3.65 (m, 4 H), 2.10 (s, 3 H), 1.86–2.09 (m, 3 H), 1.65 (m, 1 H); ^{13}C NMR δ 171.7, 66.7, 60.8, 48.8, 28.2, 24.2, 22.8.

(*S*)-1-Acetyl-2-(chloromethyl)pyrrolidine (11).[30] Alcohol **10** (13.01 g; 90.9 mmol) was dissolved in chloroform (260 mL), brought to approximately 0 °C, and thionyl chloride (16.0 mL, 150 mol %) was added dropwise over 10 min. The solution was stirred at 0 °C for 4.5 h, concentrated to a yellow residue by rotary evaporation (bath temperature <30 °C), redissolved in $CHCl_3$ (50 mL), and then chilled to 0 °C. Triethylamine (approximately 15 mL) was added dropwise until fuming had ceased, and the solvent was removed under reduced pressure. Addition of Et_2O (300 mL) resulted in precipitation of solids. Norit decolorizing charcoal was added and the mixture was stirred overnight. The mixture was filtered, and the filtrate was concentrated and then Kugelrohr distilled (80–100 °C, 0.8 mmHg; ice bath cooling of receiving bulb) to yield of **11** (11.63 g, 79%) as a yellow oil (lit.[30] bp 90–94 °C, 1 mmHg). The oil was homogeneous by TLC (R_f = 0.51; $CH_3OH/CHCl_3$, 1:9; ninhydrin development): ^{1}H NMR δ 4.31 (m, 1 H), 3.66–3.77 (m, 2 H), 3.44–3.55 (m, 2 H), 2.07 (s, 3 H), 1.97–2.06 (m, 2 H), 1.87–1.97 (m, 2 H); ^{13}C NMR δ 169.6, 59.5, 48.4, 44.8, 27.8, 23.9, 22.8.

(*S*)-1-Acetyl-2-(azidomethyl)pyrrolidine (12).[30] The chloride **11** (11.63 g, 72.0 mmol) was dissolved in DMF (172 mL). After sodium azide (9.36 g; 200 mol %) and potassium iodide (1.08 g; 10 mol %) were added to the solution, the mixture was brought to 110 °C (external) and stirred for 8 h. The reaction mixture was cooled (20 °C) and the DMF was removed by rotary evaporation (35–40 °C, 0.5 mmHg), leaving a residue which was dissolved in CH_2Cl_2 (150 mL). The salts were removed by filtration, and the filtrate was evaporated to provide 17 g of a crude yellow liquid. The remaining residual DMF was removed by Kugelrohr distillation (70–72 °C, 0.5 mmHg) leaving 11 g of a yellow residual liquid which was mixed in $CHCl_3$ (50 mL) and filtered through a Rainin Nylon-66 (0.45 μm) filter. Evaporation of solvent afforded **12** (10.59 g, 87%) as a yellow liquid which was used without further purification in the next reaction: ^{1}H NMR δ 4.21 (m, 1 H), 3.37–3.70 (m, 4 H), 2.07 (s, 3 H), 1.88–2.12 (m, 4 H); IR (neat) 2090, 1610, cm^{-1}.

(*S*)-2-(Aminomethyl)-1-ethylpyrrolidine (13).[30] A flask was charged with Et_2O (330 mL) and $LiAlH_4$ (14.3 g, 600 mol %) and then cooled (0 °C). The azide **12** (10.60 g, 63.0 mmol) dissolved in Et_2O (25 mL) was added to the reaction mixture over 15 min. After addition was complete, the solution was warmed to 50 °C (external) for 8 h. The reaction mixture was cooled to 0 °C, and then 10% aqueous potassium sodium tartrate (27.1 mL) was carefully added (dropwise) over 2.75 h. The mixture was stirred over 1 h (0 °C), brought to room temperature, and then suction filtered. The solids were washed with Et_2O (3 × 150 mL) and the combined Et_2O phases were concentrated by rotary evaporation (bath temperature <30 °C; water aspirator vacuum, ca. 125 mmHg) to afford 7.00 g of a pale yellow liquid. Distillation (96–100 °C; water aspirator vacuum, ca. 125 mmHg) of the liquid through a short (2 cm) fractionation column yielded **13** (6.03 g, 75%) as a clear liquid (lit.[11] bp 78–80 °C, 25 mmHg). For optical purity analysis see below. Significant losses of material occur if the bath temperature of the rotary evaporator exceeds 30 °C or if pressures lower than that produced by a water aspirator are used. ^{1}H and ^{13}C NMR spectra were identical with those obtained from a sample of commercially available racemic material: ^{1}H NMR δ 3.16 (m, 1 H), 2.82 (m, 1 H), 2.73 (dd, 1 H, J = 12.7, 3.6), 2.67 (dd, 1 H, J = 12.7, 6.2), 2.34 (m, 1 H), 2.11–2.23 (m, 2 H), 1.88 (m, 1 H), 1.73 (m, 2 H), 1.60 (m, 1 H), 1.44 (br s, 2 H), 1.10 (t, 3 H, J = 7.2); ^{13}C NMR δ 66.1, 53.8, 48.6, 44.7, 28.1, 22.6, 13.9.

Optical Purity of 13. A solution of (*R*)-(+)-α-methoxy-α-[(trifluoromethyl)phenyl]acetic acid[35] (MPTA acid; 126.6 mg; 0.5406 mmol) in CH_2Cl_2 (2.5 mL) was cooled (0 °C) and oxalyl chloride (0.12 mL, 250 mol %) was added, followed by DMF (8.4 μL, 20 mol %). After stirring for 1 h at room temperature, the reaction mixture was concentrated on a rotary evaporator (bath temperature ca. 40 °C) and redissolved in CH_2Cl_2 (2.5 mL), and then the pyrrolidine **13** (0.20 mL, 250 mol %) was added. The reaction was stirred for 5 min (20 °C), and then CH_2Cl_2 (10 mL) and 5% aqueous $NaHCO_3$ (0.20 mL, 250 mol %) were added. The layers were separated, the aqueous layer was washed with CH_2Cl_2 (2 × 5 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the MPTA amide **14** (178.1 mg, 96%) as a viscous yellow oil: TLC R_f = 0.32 (variable); $CH_3OH/CHCl_3$, 1:9; ^{1}H NMR δ 7.57 (m, 2 H), 7.39 (m, 3 H), 7.18 (br s, 1 H), 3.53 (ddd, 1 H, J = 13.7, 7.2, 3.3), 3.45 (d, 3 H, J = 1.4), 3.23 (dt, 1 H, J = 13.6, 4.1), 3.11 (br t, 1 H, J = 7.3), 2.79 (dq, 1 H, J = 12.0, 7.4), 2.63 (br m, 1 H), 2.26 (dq, 1 H, J = 12.0, 6.9), 2.15 (dt, 1 H, J = 9.0, 7.6), 1.81 (dq, 1 H, J = 12.2, 8.5), 1.61 (m, 1 H), 1.36–1.48 (m, 2 H), 1.10 (t, 3 H, J = 7.2). Anal. ($C_{17}H_{23}N_2O_2F_3$) C, H, N.

The racemic **13** was derivatized in an identical manner noted immediately above. The resulting ^{1}H NMR spectrum of the reaction mixture was quite complex as a result of the presence of two diastereomers. Baseline separated triplets of equal intensity were observed at 1.10 ppm and 1.02 ppm, corresponding to the methyl groups of the above-synthesized *R,S* diastereomer (**14**), and the *R,R* diastereomer, respectively. Relative intensities (integration) of these two resonances were used to quantify the diastereomeric excess of **14**, and consequently, the enantiomeric excess of **13**, was quantitated as >99.5%. Limits of detection were measured by preparing samples of **14** doped with 5%, 1%, and 0.5% quantities of *R,R* diastereomer. The diastereomeric composition of these mixtures was quantitated by the ^{1}H NMR methyl signals. These results were confirmed by capillary GLC data which separated and quantitated the *R,S* diastereomer (**14**) from the *R,R* diastereomer (retention times 46.6 min and 48.3 min, respectively; helium carrier gas flow, 20 mL/min; injector and detector temperature, 220 °C; oven temperature, 100 °C for 20 min followed by a temperature ramp, 2 °C/min, increased to 140 °C).

2-Hydroxy-3-methoxybenzoic Acid, Methyl Ester (16).[38] The 3-methoxysalicylic acid (**15**) (15.03 g, 89.4 mmol) was dissolved in methanol (250 mL), and a catalytic amount of 18 M H_2SO_4 (1 mL) was added. The mixture was warmed to reflux (98 °C, external) and stirred for 58 h. The reaction was cooled and the solvent was evaporated. The resulting residue was dissolved in CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ (100 mL), the aqueous layer was back-extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to a brown solid. Kugelrohr distillation of the crude solid (85–88 °C, 0.6 mmHg) afforded **16** (14.97 g, 92%) as a white solid, mp 61.5–62.5 °C (lit.[38] mp 63 °C), which was homogeneous by TLC (R_f = 0.54, $CHCl_3$): ^{1}H NMR δ 10.45 (s, 1 H), 7.43 (dd, 1 H, J = 8.2, 1.4), 7.05 (d, 1 H, J = 7.9), 6.82 (t, 1 H, J = 8.1), 3.95 (s, 3 H), 3.90 (s, 3 H).

3-Methoxy-2-(2-propenyloxy)benzoic Acid, Methyl Ester (17). Calcined potassium carbonate (22.68 g; 250 mol %) and allyl bromide (25.1 mL; 450 mol %) were added to a solution of ester **16** (14.57 g; 80.0 mmol) in acetone (100 mL). The solution

(67) Wyrick, S. D.; McDougald, D. L.; Mailman, R. B. *J. Labelled Compd. Radiopharm.* **1986**, *23*, 685.

was refluxed for 12 h (80 °C, external), then cooled (20 °C), diluted with Et_2O (150 mL), filtered, and then concentrated. The resulting liquid was chromatographed (gravity, silica gel, $CHCl_3$), to afford **17** as a pale yellow liquid (16.53 g, 93%), which was homogeneous by TLC (R_f = 0.39; $CHCl_3$): ^1H NMR δ 7.32 (dd, 1 H, J = 7.6, 1.9), 7.09 (t, 1 H, J = 7.9), 7.05 (dd, 1 H, J = 8.2, 1.8), 6.13 (ddt, 1 H, 17.2, 10.4, 5.8), 5.37 (dq, 1 H, J = 17.2, 1.6), 5.23 (dq, 1 H, J = 10.3, 1.3), 4.57 (dt, 2 H, J = 5.9, 1.3), 3.89 (s, 3 H), 3.87 (s, 3 H). A small sample was Kugelrohr distilled (88–90 °C, 0.5 mmHg), giving a colorless liquid which was used for elemental analysis. Anal. ($C_{12}H_{14}O_4$) C, H.

2-Hydroxy-3-methoxy-5-(2-propenyl)benzoic Acid, Methyl Ester (18). A flask containing allyl ether **17** (14.53 g, 65.4 mmol) was heated to 220 °C (external) and stirred for 45 min, after which no starting material was observed by TLC. The product (TLC R_f = 0.50; $CHCl_3$) was purified by chromatography (gravity, silica gel, $CHCl_3$), affording **18** (13.33 g, 92%) as a white solid: mp 45–46 °C; ^1H NMR δ 10.56 (s, 1 H), 7.24 (d, 1 H, J = 1.5), 6.87 (d, 1 H, J = 1.8), 5.94 (ddt, 1 H, J = 17.9, 9.2, 6.6), 5.09 (d, 1 H, J = 11.0), 5.08 (d, 1 H, J = 17.5), 3.95 (s, 3 H), 3.89 (s, 3 H), 3.32 (d, 2 H, J = 6.7). A small sample was Kugelrohr distilled (80–140 °C, 0.8 mmHg) for elemental analysis (mp 45–46 °C). Anal. ($C_{12}H_{14}O_4$) C, H.

2,3-Dimethoxy-5-(2-propenyl)benzoic Acid, Methyl Ester (19). Calcined potassium carbonate (39.83 g; 500 mol %) and methyl iodide (17.9 mL; 500 mol %) were added to a solution of **18** (12.81 g, 57.6 mmol) in acetone (120 mL). The reaction mixture was heated at reflux (70 °C, external) for 17 h. After the mixture was cooled to room temperature, Et_2O (120 mL) was added, the salts were filtered off and washed with Et_2O (2 × 50 mL), and the solvent was evaporated under reduced pressure. Kugelrohr distillation (100–170 °C, 0.6 mmHg) provided **19** (12.92 g, 95%) as a pale yellow liquid which was shown to be homogeneous by TLC (R_f = 0.32; $CHCl_3$): ^1H NMR δ 7.14 (d, 1 H, J = 2.0), 6.88 (d, 1 H, J = 2.0), 5.94 (ddt, 1 H, J = 16.9, 10.2, 6.8), 5.11 (dd, 1 H, J = 16.9, 1.6), 5.10 (dd, 1 H, J = 10.2, 1.4), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.36 (d, 2 H, J = 6.7). Anal. ($C_{13}H_{16}O_4$) C, H.

2,3-Dimethoxy-5-(3-hydroxypropyl)benzoic Acid, Methyl Ester (20). A solution of alkene **19** (3.00 g; 12.7 mmol) in THF (18 mL) was cooled (0 °C). To this solution was added 9-BBN[40] in THF (0.5 M, 37.8 mL, 149 mol %), and the mixture was stirred at 0 °C for 40 min followed by 40 min at room temperature. In some runs, the titer of the commercially available 9-BBN solution was substantially lower than claimed and additional reagent had to be added to the mixture to force the hydroboration to completion. The reaction was cooled (0 °C) then 1 M NaOH (32 mL, 250 mol %) was added over 5 min, followed by 30% aqueous hydrogen peroxide (25 mL) over 5 min. The reaction mixture was stirred at 0 °C for 30 min then room temperature for 30 min. The THF was removed by rotary evaporation, and the resulting aqueous solution was extracted with $CHCl_3$ (4 × 50 mL). The combined chloroform layers were dried (Na_2SO_4), filtered, and evaporated affording 4 g of a clear crude oil which was purified by chromatography (gravity, silica gel; EtOAc/isooctane, 1:1) to provide **20** (2.91 g, 90%) as a clear oil. The desired product (R_f = 0.08; EtOAc/isooctane, 1:2.0) was UV visible by TLC, while the higher and lower R_f non-UV active separated impurities were visualized by staining with phosphomolybdic acid: ^1H NMR δ 7.15 (d, 1 H, J = 1.9), 6.90 (d, 1 H, J = 1.9), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.68 (t, 2 H, J = 6.4), 2.69 (t, 2 H, J = 7.6), 1.89 (dt, 2 H, J = 7.7, 6.4). Anal. ($C_{13}H_{18}O_5$) C, H.

2,3-Dimethoxy-5-[3-[[(4-methylphenyl)sulfonyl]oxy]propyl]benzoic Acid, Methyl Ester (21). The alcohol **20** (1.44 g; 5.66 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with pyridine (0.59 mL, 130 mol %) and *p*-toluenesulfonyl chloride (1.13 g, 105 mol %). The reaction vessel was sealed under an argon atmosphere and refrigerated (2 °C, 24 h). The reaction solvent was evaporated, and the residue was partitioned between 0.25 M HCl (50 mL) and Et_2O (100 mL). After the layers were separated, the Et_2O phase was extracted with 0.25 M HCl (50 mL), the combined aqueous layers were back-extracted with Et_2O (2 × 25 mL), and the pooled organic layers were dried (Na_2SO_4), filtered, concentrated, and chromatographed (gravity, silica gel column; EtOAc/hexane, 1:2.0) affording **21** (1.92 g, 83%) as a yellow oil: TLC R_f = 0.24; EtOAc/hexane, 1:2.0; ^1H NMR δ 7.78 (d, 2 H, J = 8.3), 7.34 (d, 2 H, J = 8.2), 7.06 (d, 1 H, J = 2.0), 6.85 (d, 1 H, J = 1.9), 4.03 (t, 2 H, J = 6.1), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.64 (t, 2 H, J = 7.6), 2.45 (s, 3 H), 1.96 (dt, 2 H, J = 7.5, 6.2). Anal. ($C_{20}H_{24}O_7S$) C, H.

2,3-Dimethoxy-5-(3-fluoropropyl)benzoic Acid, Methyl Ester (22). Tetra-*n*-butylammonium fluoride in THF (1.1 M, 5.1 mL, 142 mol %) was added to a solution of tosylate **21** (1.61 g, 3.94 mmol) in THF (20 mL). The reaction mixture was warmed to 55 °C (external) and stirred for 1.5 h. The solution was concentrated by rotary evaporation and then triturated repeatedly with Et_2O (7 × 25 mL) until no further product appeared by TLC (R_f = 0.42; EtOAc/hexane, 1:2.0) in the Et_2O extract. The combined Et_2O extracts were concentrated, and then purified by column chromatography (gravity, silica gel, EtOAc/hexane, 1:2.0) affording **22** (0.91 g, 90%) as a colorless oil, homogeneous by TLC: ^1H NMR δ 7.15 (d, 1 H, J = 2.0), 6.90 (d, 1 H, J = 1.9), 4.46 (dt, 2 H, J = 47.2, 5.8), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 2.72 (t, 2 H, J = 7.8), 2.01 (dtt, 2 H, J = 25.6, 7.8, 6.0). A small sample was Kugelrohr distilled (120 – 200 °C, 1.5 mmHg) for elemental analysis. Anal. ($C_{13}H_{17}O_4F$) C, H.

2,3-Dimethoxy-5-(3-fluoropropyl)benzoic Acid (23). The ester **22** (0.88 g; 3.43 mmol) was dissolved in THF (30 mL), and then 0.5 M NaOH (100 mL) was added, and the solution was warmed with stirring to 80 °C (external) during which THF was allowed to slowly evaporate. After 40 min, no starting material was observed by TLC and the product (R_f = 0.20, variable; EtOAc/hexane, 1:2.0) was isolated by first washing the aqueous reaction mixture with Et_2O (40 mL), back-extracting the Et_2O layer with 1 M NaOH (100 mL), acidifying the combined aqueous layers (0 °C) to pH 2 with 4.9 M H_3PO_4, and then extracting the acidic aqueous phase with chloroform (1 × 100 mL, 5 × 25 mL). The organic portion was dried (Na_2SO_4) and filtered, and the solvent was evaporated to provide **23** (0.83 g, 100%) as a pale yellow oil which eventually formed a white solid: mp 37.0–37.5 °C; ^1H NMR δ 7.57 (d, 1 H, J = 2.0), 6.99 (d, 1 H, J = 2.0), 4.46 (dt, 2 H, J = 47.1, 5.8), 4.07 (s, 3 H), 3.93 (s, 3 H), 2.76 (t, 2 H, J = 7.8), 2.03 (dtt, 2 H, J = 25.7, 7.6, 5.8). Anal. ($C_{12}H_{15}O_4F$) C, H.

(*S*)-2,3-Dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(3-fluoropropyl)benzamide (1). The acid **23** (333.5 mg; 1.38 mmol), dissolved in CH_2Cl_2 (7 mL), was cooled to 0 °C then oxalyl chloride (0.30 mL; 250 mol %) was added, followed by DMF (21 μL, 20 mol %). The solution was stirred at 0 °C for 30 min, concentrated on a rotary evaporator (bath temperature ca. 45 °C), and the corresponding acid chloride was redissolved in CH_2Cl_2 (7 mL). The amine **13** (0.30 mL; 150 mol %) was added to the acid chloride and the solution was stirred at room temperature for 15 min. The reaction was diluted with CH_2Cl_2 (20 mL), and 5% aqueous $NaHCO_3$ (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the organic phases were combined, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure to yield a crude yellow oil (0.52 g) which was purified by flash column chromatography (silica gel; $CH_3OH/CHCl_3$, 1:19), to afford **1** (440.2 mg, 90%) as a yellow oil: TLC R_f = 0.34 (variable); $CH_3OH/CHCl_3$, 1:9. $[\alpha]^{22}_D$ = −48° (c = 2, CH_3OH); ^1H NMR δ 8.48 (br s, 1 H), 7.55 (d, 1 H, J = 2.0), 6.88 (d, 1 H, J = 2.1), 4.46 (dt, 2 H, J = 47.2, 5.9), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.78 (ddd, 1 H, J = 13.8, 7.0, 3.2), 3.33 (dt, 1 H, J = 14.0, 3.8), 3.23 (br t, 1 H, J = 7.2), 2.89 (dq, 1 H, J = 11.8, 7.4), 2.74 (t, 2 H, J = 7.7), 2.63 (br m, 1 H), 2.24 (dq, 1 H, J = 11.8, 6.8), 2.16 (dt, 1 H, J = 9.5, 7.7), 2.03 (dtt, 2 H, J = 25.5, 7.7, 6.0), 1.90 (dq, 1 H, J = 11.8, 8.7), 1.63–1.77 (m, 3 H), 1.14 (t, 3 H, J = 7.2); ^{13}C NMR δ 165.3, 152.4, 145.8, 137.2, 126.5, 122.1, 115.4, 82.9 (d, J = 164.9), 62.3, 61.1, 56.0, 53.4, 47.8, 41.0, 31.7 (d, J = 19.7), 31.1 (d, J = 5.2), 28.3, 22.5, 13.8; 135° DEPT ^{13}C NMR δ 122.1, 115.4, 82.9 (d, J = 164.9),* 62.3, 61.1, 56.0, 53.4,* 47.8,* 41.0,* 31.7 (d, J = 19.7),* 31.1 (d, J = 5.2),* 28.3,* 22.5,* 13.8. Anal. ($C_{19}H_{29}N_2O_3F$) C, H, N.

2,3-Dimethoxy-5-(2-hydroxyethyl)benzoic Acid, Methyl Ester (24). The alkene **19** (1.05 g; 4.44 mmol), dissolved in methanol (10 mL) and CH_2Cl_2 (10 mL), was cooled to −78 °C and ozone was bubbled through the solution until a faint blue color appeared. The excess ozone was purged from the reaction mixture by bubbling O_2 through the solution. Sodium borohydride (0.34 g, 200 mol %) was added and the mixture was stirred for 10 min at −78 °C and then brought to 0 °C and stirred for 30 min. An

additional amount of $NaBH_4$ (0.17 g, 100 mol %) was added and the mixture was stirred for 30 min. This last sequence was repeated once more, and then the reaction was warmed to room temperature and quenched by adding H_2O (10 mL) followed by 1 M H_3PO_4 (20 mL) with stirring. After gas evolution had ceased, the layers were separated and the aqueous portion was washed with CH_2Cl_2 (5 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, evaporated, and chromatographed (flash column, silica gel; 100% $CHCl_3$, gradient to $CH_3OH/CHCl_3$, 1:19) providing **24** (0.90 g, 84%) as a clear oil, homogeneous by TLC (R_f = 0.46; $CH_3OH/CHCl_3$, 1:9), ^1H NMR δ 7.19 (d, 1 H, J = 2.0), 6.94 (d, 1 H, J = 2.0), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.87 (t, 2 H, J = 6.3), 2.84 (t, 2 H, J = 6.4). A small sample was Kugelrohr distilled (140–145 °C, 0.3 mmHg) for microanalysis. Anal. ($C_{12}H_{16}O_5$) C, H.

2,3-Dimethoxy-5-(2-fluoroethyl)benzoic Acid, Methyl Ester (26). The alcohol **24** (174.3 mg; 0.726 mmol), dissolved in CH_2Cl_2 (5 mL), was treated with 2,6-lutidine (0.21 mL, 250 mol %) then cooled (0 °C) and allowed to react with trifluoromethanesulfonic anhydride (0.42 mL, 350 mol %). After the mixture stirred for 0.5 h (0 °C), the starting material had been completely replaced by a higher R_f material by TLC (R_f = 0.32; EtOAc/hexane, 1:2.0) and the reaction was quenched by adding H_2O (5 mL) followed by saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic portions were washed with 1 M H_3PO_4 (10 mL). After the aqueous phase was back-extracted with CH_2Cl_2 (3 × 5 mL), the combined organic solutions were dried (Na_2SO_4), filtered, and evaporated, affording the triflate **25** (yellow oil) which was used directly in the next reaction.

A solution the crude triflate **25** in THF (5 mL) was treated with tetra-*n*-butylammonium fluoride in THF (1 M, 1.46 mL; 200 mol %). The reaction was stirred for 25 min at room temperature, filtered through a pad (1.3 × 3 cm) of gravity silica gel, then concentrated, and chromatographed (gravity column, silica gel; EtOAc/hexane, 1:3) to afford **26** (143.7 mg, 82% from **24**) as a yellow oil. TLC showed the fluoride **26** to have an identical R_f value with triflate **25**: ^1H NMR δ 7.19 (d, 1 H, J = 2.0), 6.94 (d, 1 H, J = 1.9), 4.63 (dt, 2 H, J = 47.0, 6.3), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 2.98 (dt, 2 H, J = 24.5, 6.3). Anal. ($C_{12}H_{15}O_4F$) C, H.

2,3-Dimethoxy-5-(2-fluoroethyl)benzoic Acid (28). The 5-(fluoroethyl) methyl ester **26** was saponified in direct analogy to the analogue **23**. The benzoic acid was isolated (140.0 mg, 92%) as a white solid: mp 50–52 °C; ^1H NMR δ 7.55 (d, 1 H, J = 2.1), 7.06 (d, 1 H, J = 2.0), 4.65 (dt, 2 H, J = 47.0, 6.2), 4.06 (s, 3 H), 3.93 (s, 3 H), 3.01 (dt, 2 H, J = 25.3, 6.1). Anal. ($C_{11}H_{13}O_4F$) C, H.

(*S*)-2,3-Dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(2-fluoroethyl)benzamide (2). The coupling of acid **28** to the amine **13** and subsequent purification was achieved in direct analogy to that described for **1**, affording amide **2** (229.9 mg, 88%) as a yellow oil: TLC R_f = 0.21 (variable); $CH_3OH/CHCl_3$, 1:9; $[\alpha]^{22}_D$ = −53° (c = 2, CH_3OH); ^1H NMR δ 8.43 (br s, 1 H), 7.58 (d, 1 H, J = 2.0), 6.92 (d, 1 H, J = 2.0), 4.64 (dt, 2 H, J = 47.0, 6.4), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.78 (ddd, 1 H, J = 13.8, 7.2, 2.5), 3.31 (ddd, 1 H, 13.8, 5.2, 2.8), 3.11 (dt, 1 H, J = 6.1, 3.0), 3.01 (dt, 2 H, J = 24.2, 6.4), 2.88 (dq, 1 H, J = 11.9, 7.4), 2.63 (br m, 1 H), 2.23 (dq, 1 H, J = 12.0, 7.0), 2.16 (q, 1 H, J = 8.7), 1.91 (dq, 1 H, J = 12.6, 8.1), 1.62–1.79 (m, 3 H), 1.13 (t, 3 H, J = 7.2); ^{13}C NMR δ 165.2, 152.5, 146.3, 133.4 (d, J = 5.9), 126.5, 122.7, 115.9, 83.9 (d, J = 169.1), 62.3, 61.2, 56.0, 53.5, 47.8, 41.0, 36.6 (d, J = 20.2), 28.3, 22.5, 13.9; 135° DEPT ^{13}C NMR δ 122.7, 115.9, 83.9 (d, J = 169.1),* 62.3, 61.2, 56.0, 53.5,* 47.8,* 41.0,* 36.6 (d, J = 20.2),* 28.3,* 22.5,* 13.9. Anal. ($C_{18}H_{27}N_2O_3F$) C, H.

A sample of (*R*)-**2** was similarly synthesized: $[\alpha]^{22}_D$ = +51° (c = 2, CH_3OH).

1,2-Dimethoxy-4-(methoxymethoxy)benzene (30). The commercially available 3,4-dimethoxyphenol **29** (25.85 g, 0.1677 mol) was dissolved in THF (120 mL), cooled to 0 °C, and then *n*-BuLi (2.5 M in hexane, 67 mL, 100 mol %) was added dropwise (10 min). The solution was stirred for 2.5 h at 0 °C and then chloromethyl methyl ether (1.27 mL, 100 mol %, **Caution**: carcinogen) was added. Stirring was continued at 0 °C for 0.5 h followed by room temperature for 2.5 h. Water (70 mL) was added and the THF was evaporated off by rotary evaporation. The aqueous solution was washed with Et_2O (1 × 150 mL; 3 × 40 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (gravity, silica gel, $CHCl_3$), providing **30** (25.76 g, 73%) as a clear liquid, homogeneous by TLC (R_f = 0.42; $CHCl_3$); ^1H NMR δ 6.77 (d, 1 H, J = 8.7), 6.63 (d, 1 H, J = 2.7), 6.59 (dd, 1 H, J = 8.7, 2.8), 5.12 (s, 2 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.49 (s, 3 H). A small sample was Kugelrohr distilled for microanalysis (107–110 °C, 0.7 mmHg). Anal. ($C_{10}H_{14}O_4$) C, H.

2,3-Dimethoxy-6-(methoxymethoxy)benzoic Acid (31). Diethyl ether (135 mL) was cooled to 0 °C, and *n*-BuLi (2.5 M in hexane, 55 mL, 105 mol %) was added, followed by TMEDA (20.6 mL, 105 mol %). After the mixture was stirred for 10 min, a solution of **30** (25.76 g, 0.1300 mol) in Et_2O (25 mL) was added. The reaction mixture was stirred at 0 °C for 1 h. The white, heterogeneous mixture was transferred all at once to a 1-L flask containing Et_2O (200 mL) and freshly crushed dry ice (60 g). The mixture was allowed to stir until room temperature was reached, then H_2O (200 mL) was added, layers were separated, and the organic phase was washed with 1 M NaOH (3 × 35 mL). The combined aqueous layers were cooled with an ice bath and acidified to pH 1.5 with 4.9 M H_3PO_4. After extraction with chloroform (5 × 50 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to afford **31** (28.46 g, 90%) as a white solid: mp 75–77 °C; ^1H NMR δ 6.92 (d, 1 H, J = 9.1), 6.89 (d, 1 H, J = 9.1), 5.16 (s, 2 H), 3.94 (s, 3 H), 3.85 (s, 3 H), 3.51 (s, 3 H). Anal. ($C_{11}H_{14}O_6$) C, H.

2,3-Dimethoxy-6-hydroxybenzoic Acid, Phenylmethyl Ester (32). The acid **31** (15.00 g; 75.69 mmol) was dissolved in CH_2Cl_2 (150 mL) and cooled to 0 °C, and DMF (11.7 mL, 200 mol %) was added followed by the dropwise addition of oxalyl chloride (13.2 mL, 200 mol %) over 15 min. After the mixture was stirred for 1 h, benzyl alcohol (31.3 mL, 400 mol %) was added. The reaction was stirred for 1.5 h at 0 °C, and then worked up by adding of 5% aqueous $NaHCO_3$ (150 mL), separating the phase, and washing the aqueous phase with CH_2Cl_2 (5 × 40 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation followed by Kugelrohr distillation (70 °C, 0.9 mmHg), affording 22.5 g of a crude yellow liquid. The liquid was dissolved in a minimal amount of ethyl acetate and purified (TLC R_f = 0.46; EtOAc/isooctane; 1:1) by gravity column chromatography (silica gel; EtOAc/isooctane, 1:5.7), yielding **32** (20.79 g, 95%) as a pale yellow solid. For microanalysis, the product was recrystallized from isooctane/EtOAc, affording a white solid: mp 70–71 °C; ^1H NMR δ 10.50 (s, 1 H), 7.49 (d, 2 H, J = 7.0), 7.35–7.41 (m, 3 H), 7.08 (d, 1 H, J = 9.1), 6.71 (d, 1 H, J = 9.1), 5.43 (s, 2 H), 3.82 (s, 3 H), 3.73 (s, 3 H). Anal. ($C_{16}H_{16}O_5$) C, H.

2,3-Dimethoxy-6-(2-propenoxy)benzoic Acid, Phenylmethyl Ester (33). Compound **33** was formed by using the method described for generation of allyl ether **17**. The crude material was purified by flash chromatography (silica gel; EtOAc/isooctane, 1:6.7), affording **33** (17.12 g, 83%) as a light yellow oil: TLC R_f = 0.44 (EtOAc/isooctane, 1:1); ^1H NMR δ 7.45 (d, 2 H, J = 6.9), 7.35 (t, 2 H, J = 6.9), 7.33 (d, 1 H, J = 7.1), 6.85 (d, 1 H, J = 9.0), 6.58 (d, 1 H, J = 9.0), 5.94 (ddt, 1 H, J = 17.3, 10.4, 5.2), 5.39 (s, 2 H), 5.32 (dq, 1 H, J = 17.3, 1.6), 5.21 (dq, 1 H, J = 10.6, 1.4), 4.48 (dt, 2 H, J = 5.1, 1.6), 3.81 (s, 3 H), 3.80 (s, 3 H). Anal. ($C_{19}H_{20}O_5$) C, H.

2,3-Dimethoxy-6-hydroxy-5-(2-propenyl)benzoic Acid, Phenylmethyl Ester (34). Allyl ether **33** was heated to 200–205 °C (external) for 15 min. After the mixture was cooled to room temperature, the sides of reaction flask were washed with CH_2Cl_2 and then the solution was concentrated by rotary evaporation. The liquid was resubjected to thermolysis for an additional 15 min. This sequence was repeated one more time, after which the crude product was purified by column chromatography (gravity silica gel column; EtOAc/isooctane, 1:4), providing phenol **34** (12.28 g, 88%) as a yellow liquid which was homogeneous by TLC (R_f = 0.55; EtOAc/isooctane, 1:1); ^1H NMR δ 10.76 (s, 1 H), 7.48 (d, 2 H, J = 7.1), 7.39 (t, 2 H, J = 7.0), 7.35 (d, 1 H, J = 7.1), 6.98 (s, 1 H), 5.98 (ddt, 1 H, J = 16.4, 10.8, 6.6), 5.43 (s, 2 H), 5.09 (dd, 1 H, J = 16.7, 1.6), 5.08 (dd, 1 H, J = 10.8, 1.3), 3.81 (s, 3 H), 3.71 (s, 3 H), 3.38 (d, 2 H, J = 6.6). Anal. ($C_{19}H_{20}O_5$) C, H.

2,3-Dimethoxy-6-[(2-methoxyethoxy)methoxy]-5-(2-propenyl)benzoic Acid, Phenylmethyl Ester (35). Sodium hydride (1.10 g of a 60% (w/w) mineral oil suspension; 150 mol %) was washed with isooctane (3 × 20 mL) and with THF (15 mL) and then suspended in 30 mL of THF at 0 °C. The phenol **34** (6.00 g; 18.3 mmol), dissolved in THF (20 mL), was added dropwise over 5 min, and the reaction was allowed to stir for 30 min at 0 °C before adding (2-methoxyethoxy)methyl chloride (3.1 mL, 150 mol %). After the reaction was allowed to warm to room temperature over a period 1 h, the solution was again cooled with an ice bath and quenched by slow addition of 1 M NaOH (40 mL). The THF was removed by rotary evaporation, and the product was dissolved into CH_2Cl_2 (5 × 40 mL), dried (Na_2SO_4), filtered, and concentrated. Purification of the crude material by column chromatography (gravity silica gel; EtOAc/isooctane, 1:1) provided **35** (7.62 g, 100%) as a yellow liquid: TLC R_f = 0.43; EtOAc/isooctane, 1:1; ^{1}H NMR δ 7.46 (d, 2 H, J = 7.2), 7.36 (t, 2 H, J = 7.3), 7.32 (d, 1 H, J = 7.2), 6.75 (s, 1 H), 5.92 (ddt, 1 H, J = 17.8, 9.4, 6.6), 5.37 (s, 2 H), 5.09 (d, 1 H, J = 11.4), 5.08 (dd, 1 H, J = 16.6, 1.6), 4.96 (s, 2 H), 3.82 (s, 3 H), 3.78 (m, 2 H), 3.75 (s, 3 H), 3.53 (m, 2 H), 3.41 (d, 2 H, J = 6.5), 3.37 (s, 3 H). Anal. ($C_{23}H_{28}O_7$) C, H.

2,3-Dimethoxy-5-(3-hydroxypropyl)-6-[(2-methoxyethoxy)methoxy]benzoic Acid, Phenylmethyl Ester (36). The hydroboration of **35** (2.99 g, 7.18 mmol) was analogous to the preparation described for **20**, except the chromatography solvent system was EtOAc/isooctane, 2.0:1; followed by EtOAc, to afford the pure propanol **36** (2.73 g, 88%): TLC R_f = 0.35; EtOAc; ^{1}H NMR δ 7.46 (d, 2 H, J = 7.3), 7.37 (t, 2 H, J = 7.0), 7.33 (d, 1 H, J = 7.2), 6.77 (s, 1 H), 5.37 (s, 2 H), 4.94 (s, 2 H), 3.83 (s, 3 H), 3.80 (m, 2 H), 3.75 (s, 3 H), 3.64 (q, 2 H, J = 5.9), 3.56 (m, 2 H), 3.38 (s, 3 H), 2.76 (t, 2 H, J = 7.7), 2.21 (t, 1 H, J = 6.0), 1.83 (dt, 2 H, J = 7.6, 6.1). Anal. ($C_{23}H_{30}O_8$) C, H.

2,3-Dimethoxy-6-[(2-methoxyethoxy)methoxy]-5-[3-[[(4-methylphenyl)sulfonyl]oxy]propyl]benzoic Acid, Phenylmethyl Ester (37). The tosylate **37** was prepared by using the procedure described for **21**, except that chromatography was performed by using a flash silica gel column, with EtOAc/isooctane as eluent, 1:2.0, yielding **37** (1.04 g, 92%) as a clear oil, homogeneous by TLC (R_f = 0.20; EtOAc/isooctane, 1:1): ^{1}H NMR δ 7.78 (d, 2 H, J = 8.3), 7.45 (d, 2 H, J = 7.4), 7.37 (t, 2 H, J = 7.0), 7.32–7.35 (m, 3 H), 6.72 (s, 1 H), 5.35 (s, 2 H), 4.90 (s, 2 H), 4.02 (t, 2 H, J = 6.1), 3.82 (s, 3 H), 3.75 (m, 2 H, overlap), 3.74 (s, 3 H, overlap), 3.51 (m, 2 H), 3.35 (s, 3 H), 2.70 (t, 2 H, J = 7.6), 2.44 (s, 3 H), 1.94 (dt, 2 H, J = 7.6, 6.1). While the sample was drying at 60 °C for microanalysis, decomposition was observed. High-resolution FAB MS m/z calcd for $C_{30}H_{37}O_{10}S$ (MH^+) 589.2107, found 589.2086.

2,3-Dimethoxy-5-(3-fluoropropyl)-6-[(2-methoxyethoxy)methoxy]benzoic Acid, Phenylmethyl Ester (38). The fluoride **38** was prepared in a similar fashion to that described for **22** except that purification was achieved by flash column chromatography (EtOAc/isooctane, 1:1), affording **38** (0.54 g, 97%) as a colorless oil: TLC R_f = 0.28; EtOAc/isooctane, 1:1; ^{1}H NMR δ 7.46 (d, 2 H, J = 6.9), 7.37 (t, 2 H, J = 6.9), 7.34 (d, 1 H, J = 7.1), 6.76 (s, 1 H), 5.37 (s, 2 H), 4.95 (s, 2 H), 4.46 (dt, 2 H, J = 47.3, 5.8), 3.83 (s, 3 H), 3.79 (m, 2 H), 3.74 (s, 3 H), 3.54 (m, 2 H), 3.37 (s, 3 H), 2.77 (dt, 2 H, J = 7.8, 1.8), 1.98 (ddt, 2 H, J = 26.1, 7.8, 5.9). Anal. ($C_{23}H_{29}O_7F$) C, H.

2,3-Dimethoxy-5-(3-fluoropropyl)-6-[(2-methoxyethoxy)methoxy]benzoic Acid (39). The benzyl ester **38** (0.46 g; 1.05 mmol) was dissolved in degassed methanol (20 mL), 10% (w/w) palladium on activated carbon (0.05 g) was added, and the mixture was hydrogenated under a hydrogen-filled balloon, with stirring, for 2 h at room temperature. The catalyst was removed by filtration through Celite and the solvent evaporated to yield acid **39** (0.36 g, 99%) as a yellow oil: ^{1}H NMR δ 6.81 (s, 1 H), 5.09 (s, 2 H), 4.48 (dt, 2 H, J = 47.2, 5.8), 3.91 (s, 3 H), 3.89 (m, 2 H), 3.86 (s, 3 H), 3.61 (m, 2 H), 3.41 (s, 3 H), 2.76 (t, 2 H, J = 7.7), 2.00 (ddt, 2 H, J = 26.3, 7.6, 5.8). Anal. ($C_{16}H_{23}O_7F$) C, H.

(*S*)-2,3-Dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(3-fluoropropyl)-6-[(2-methoxyethoxy)methoxy]benzamide (40). The acid **39** (0.36 g; 1.04 mmol) was dissolved in THF (10 mL) and DMF (0.16 mL, 200 mol %) and brought to 0 °C, and then oxalyl chloride (0.18 mL, 200 mol %) was added dropwise over 5 min. The reaction was stirred at 0 °C for 30 min, concentrated on a rotary evaporator (bath temperature ca. 35 °C), and redissolved in THF (3 mL), then pyrrolidine **13** (0.45 mL, 300 mol %) was added, and the reaction mixture was stirred for 30 min at room temperature. The reaction was worked up by the addition of 5% aqueous $NaHCO_3$ (10 mL), removal of the THF by rotary evaporation, and extraction with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated down to afford 0.55 g of a crude yellow oil. Flash chromatography purification of the crude material (silica gel; $CH_3OH/CHCl_3$, 1:19) provided **40** (0.21 g, 44%) as a yellow oil: TLC R_f = 0.29 (variable); $CH_3OH/CHCl_3$, 1:9; ^{1}H NMR δ 6.74 (s, 1 H), 6.35 (br s, 1 H), 5.09 (AB q, 2 H, J = 6.0, $\Delta\nu$ = 7.0 Hz), 4.48 (dt, 2 H, J = 47.3, 5.8), 3.85–3.89 (m, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.77 (ddd, 1 H, J = 13.5, 7.7, 2.5), 3.57 (t, 2 H, J = 4.7), 3.38 (s, 3 H), 3.21–3.24 (br m, 1 H), 3.11 (br m, 1 H), 2.74–2.85 (m, 3 H), 2.60 (br m, 1 H), 2.19 (dq, 1 H, J = 12.0, 6.9), 2.12 (dt, 1 H, J = 9.8, 7.7), 2.00 (dtt, 2 H, J = 26.0, 7.9, 5.9), 1.89 (m, 1 H), 1.70 (m, 3 H), 1.07 (t, 3 H, J = 7.2). Anal. ($C_{23}H_{37}N_2O_6F$) C, H, N.

(*S*)-2,3-Dimethoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(3-fluoropropyl)-6-hydroxybenzamide (3). The MEM-protected benzamide **40** (0.19 g; 0.416 mmol) was dissolved in CH_2Cl_2 (4 mL), brought to 0 °C, and $TiCl_4$ in CH_2Cl_2 (1 M, 2.1 mL, 500 mol %) was added over 1 min. After the mixture was stirred for 40 min, 5% aqueous $NaHCO_3$ (50 mL) was added (slowly at first) and the solution was allowed to warm to room temperature. The reaction mixture was extracted with CH_2Cl_2 (1 × 50 mL; 4 × 20 mL); the emulsion stayed mainly in the aqueous phase. The organic portions were combined, dried (Na_2SO_4), filtered, evaporated, and purified by flash chromatography (silica gel; $CH_3OH/CHCl_3$, 1:9), affording **3** (0.13 g, 85%) as a yellow oil: TLC R_f = 0.42 (variable); $CH_3OH/CHCl_3$, 1:9; $[\alpha]^{22}_D$ = −52° (c = 2, CH_3OH); ^{1}H NMR δ 11.83 (s, 1 H), 9.07 (br s, 1 H), 6.92 (s, 1 H), 4.48 (dt, 2 H, J = 47.4, 6.0), 3.90 (s, 3 H), 3.84 (s, 3 H), 3.75 (ddd, 1 H, J = 13.8, 7.1, 2.1), 3.29 (ddd, 1 H, J = 13.9, 4.6, 2.6), 3.21 (dt, 1 H, J = 8.3, 5.3), 2.86 (dq, 1 H, J = 12.0, 7.4), 2.73 (t, 2 H, J = 7.5), 2.63 (br m, 1 H), 2.23 (dq, 1 H, J = 11.9, 7.0), 2.17 (dt, 1 H, J = 8.8, 8.6), 2.02 (dtt, 2 H, J = 25.6, 7.4, 6.1), 1.91 (dq, 1 H, J = 11.9, 8.1), 1.71–1.77 (m, 2 H), 1.64 (dq, 1 H, J = 10.2, 7.0), 1.13 (t, 3 H, J = 7.2); ^{13}C NMR δ 170.0, 154.7, 146.4, 143.6, 125.0, 119.7, 107.6, 83.5 (d, J = 163.9), 61.9, 61.2, 56.9, 53.4, 47.7, 40.3, 30.0 (d, J = 19.6), 28.2, 25.9 (d, J = 5.5), 22.5, 13.9; 135° DEPT ^{13}C NMR δ 119.7, 83.5 (d, J = 163.9),* 61.9, 61.2, 56.9, 53.4,* 47.7,* 40.3,* 30.0 (d, J = 19.6),* 28.2,* 25.9 (d, J = 5.5),* 22.5,* 13.9. Anal. ($C_{19}H_{29}N_2O_4F$) C, H, N.

A sample of (*R*)-**3** was similarly synthesized: $[\alpha]^{22}_D$ = +48° (c = 2, CH_3OH).

2,3-Dimethoxy-5-(2-hydroxyethyl)-6-[(2-methoxyethoxy)methoxy]benzoic Acid, Phenylmethyl Ester (41). The alkene **35** was ozonized, worked up, and purified as described for the generation of **24**. The ester **41** was obtained as a yellow oil (3.82 g; 94%): TLC R_f = 0.40; EtOAc; ^{1}H NMR δ 7.45 (d, 2 H, J = 7.6), 7.37 (t, 2 H, J = 7.4), 7.34 (d, 1 H, J = 7.3), 6.79 (s, 1 H), 5.36 (s, 2 H), 4.91 (s, 2 H), 3.84 (s, 3 H), 3.77–3.84 (m, 4 H), 3.75 (s, 3 H), 3.59 (m, 2 H), 3.39 (s, 3 H), 2.92 (t, 2 H, J = 7.0). Anal. ($C_{22}H_{28}O_8$) C, H.

2,3-Dimethoxy-5-(2-fluoroethyl)-6-[(2-methoxyethoxy)methoxy]benzoic Acid, Phenylmethyl Ester (43). A solution of diethylaminosulfur trifluoride[51] (0.17 mL, 115 mol %) in CH_2Cl_2 (1.6 mL) was cooled to −78 °C, and a solution of alcohol **41** (480.2 mg, 1.142 mmol) in CH_2Cl_2 (1.6 mL) was added dropwise over 2 min. The reaction mixture was allowed to warm to room temperature and then was heated to 42 °C (external) for 5.25 h. After the mixture was cooled to room temperature, 15 mL each of CH_2Cl_2 and H_2O were added, the layers were separated, and the aqueous phase was extracted with additional CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (15 mL), the aqueous phase was back-extracted with CH_2Cl_2 (2 × 10 mL), and the combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and evaporated, and the resultant residue was chromatographed (flash, silica gel; EtOAc/isooctane, 1:4) giving 225.8 mg of a crude yellow oil (TLC R_f = 0.32; EtOAc/isooctane, 1:1) which was further purified by HPLC (EtOAc/hexane, 1:4). The less polar component was isolated as a yellow oil and was identified as benzofuran **42** (54.8 mg; 15%): ^{1}H NMR δ 7.46 (d,

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The final incubation mixtures were filtered through glass fiber filter mats by using a Skatron cell harvester. Filters were allowed to dry and 3.0 mL of Scintiverse E (Fisher Scientific) was added. After the mixture was shaken for 30 min, the radioactivity concentration was determined by an LKB RackBeta liquid scintillation counter. Data were analyzed by custom computer software, and compared, in selected cases, to that obtained from EDBA-LIGAND. Tissue protein levels were estimated by using the Folin reagent method of Lowry adapted to a Technicon Autoanalyzer I (Tarrytown, NY).

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Synthesis and Biological Activity of New Halo-Steroidal Antiestrogens

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Antiestrogen therapy is the most widely used endocrine manipulation for the treatment of breast cancer, especially in postmenopausal women. Unfortunately, the compounds presently available possess mixed agonistic/antagonistic activity, thus potentially limiting their therapeutic efficacy. Following the observations that an aliphatic chain at the 7α-position of 17β-estradiol does not prevent binding to the estrogen receptor while halogenation of estradiol can increase the affinity of its binding (expressed as RBA) to the estrogen receptor, we have synthesized a series of new steroidal antiestrogens (**6–10**) which possess both an 7α-undecanamide group and an halogen atom (Cl, Br, or I) at the 16α-position. The stereochemistry of these compounds was unambiguously established by high-field (400-MHz) nuclear magnetic resonance. Some of the compounds obtained possess potent in vivo antiestrogenic activity. At the low twice daily 3-μg dose, 16α-chloro 3,17β-diol amide, 16α-iodo 3,17β-diol amide, 16α-bromo 3,17β-diol amide, 16α-chloro 3,17α-diol amide, and 16α-bromo 3,17α-diol amide inhibit by 74, 63, 52, 35, and 60%, respectively, the estradiol-induced stimulation of uterine weight in ovariectomized Balb/c mice while 78–99% blockade of estradiol action is achieved at the 20-μg dose. These new antiestrogens show no estrogenic activity on uterine weight at the doses used while tamoxifen (2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethanamine) shows full estrogenic activity and is only a weak partial antiestrogen in the same assay.

Introduction

Breast cancer is the most frequent cancer in women. In fact, one out of 11 women in North America suffers from breast cancer during her life time while more than 50 000 women die annually from this disease.[1] Unfortunately, the present therapies show positive results in only a proportion of cases and, when present, the positive response is of short duration.[2-4] Since the first evidence for a role of estrogens in breast cancer,[5] considerable attention has been given to the mechanisms involved.[2-4] Based on the well-known observations that the action of estrogens in target tissues requires binding to the estrogen receptor,[6] a logical approach for the treatment of estrogen-sensitive breast cancer is the use of a compound which could block the interaction of estrogens with their specific receptor. In fact, such compounds, called antiestrogens, are presently used with some success for the treatment of breast cancer.[4]

However, antiestrogens devoid of estrogenic activity and thus possessing the characteristics of pure antiestrogens have not yet been made available for clinical use. The nonsteroidal antiestrogen routinely used in the endocrine therapy of breast cancer, namely tamoxifen (2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethanamine)[7,8] behaves as a mixed agonist/antagonist of estrogen action, thus limiting its therapeutic potential. Similarly, the benzothiophene derivatives LY117018[9] [6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl)][4-[2-(1-pyrrolidinyl)ethoxy]phenyl]methanone and keoxifene (LY156758)[10] ([6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thien-3-yl][4-(2-(1-piperidinyl)ethoxy)phenyl]methanone hydrochloride display significant uterotrophic activity in the rat. Recently, based on estradiol derivatives originally developed for purification of the estrogen receptor by affinity chromatography,[11] it has been observed that a series of 7α-alkyl derivatives of 17β-estradiol[12] display significant antagonistic activity in various systems, including the rat uterus and human breast cancer cells.[12,13]

On the other hand, Heiman et al.[14] and Fevig et al.[15] have reported that halogenation of the D ring of the steroid nucleus, especially at the 16α-position, results in compounds having affinities for the lamb and rat uterine estrogen receptors which are higher than 17β-estradiol itself. On the basis of this knowledge, we have synthesized a

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